the maximum or minimum points are each of salts containing water of crystallization. A simple calculation will show however that in no case is the amount of water introduced in this way enough to change the concentration of the solvent sufficiently to account for the irregularities. The connection between the water of crystallization and the maximum or minimum point of these three curves is still less noteworthy when it is considered that boric and camphoric acids which contain no water of crystallization show under similar circumstances minimum or maximum points respectively in their solubility curves.[1]

Of the determinations shown in the accompanying table, some agree fairly well with the results quoted by the United States Pharmacopoeia while others differ very considerably. In order to show such comparative values to better advantage they have been brought together in the following table and are given in the terms used for the pharmacopoeial data, that is, the part of solvent required to dissolve one part of salt.

TABLE SHOWING THE PRESENT DETERMINATIONS AS COMPARED WITH THOSE QUOTED BY THE U. S. PHARMACOPOEIA.

	Parts of solvent to dissolve 1 part of salicylate at 25°.			
	In water.		In 92.3 wt. per cent. alcohol.	
Salicylate.	Present results.	U. S. P. results.	Present results.	U. S. P. results.
Ammonium salicylate....	0.97	0.9	2.33	2.3
Lithium "	0.786	very soluble	1.193	very soluble
Phenyl "	6665.0	2333.0	4.65	5.0
Quinine "	1538.0	77.0	20.65	11.0
Salicylic acid.....	453.0	308.0	2.13	2.0
Sodium salicylate	0.867	0.8	7.33	5.5
Strontium "	18.85	18.0	48.51	66.0
Bismuth sub "	10,000.0	....	625.0	....

[DIVISION OF PHARMACOLOGY, HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH AND MARINE-HOSPITAL SERVICE, WASHINGTON, D. C.]

METHODS FOR THE DETERMINATION OF SALICYLATES.

BY ATHERTON SEIDELL.

Received June 1, 1909.

In the course of the examination of the several salicylates used for the solubility determinations described in an accompanying paper it seemed desirable to base the analyses of the samples upon a determination of the salicylic radicle. The two methods which have so far been proposed for this purpose are the Messinger and Vortmann iodine method, and the Freyer bromate method. The experiments described in the present paper show that neither of these methods are dependable and that even with the most careful control of the conditions, accurate determinations are not obtained with certainty.

[1] Seidell, *Proc. Am. Electrochem. Soc.*, Albany Meeting, 1908.

The Bromate Method.—This method which, according to Fresenius and Grünhut,[1] was first proposed by Freyer[2] was tested by them in comparison with the iodometric method of Messinger and Vortmann and the gravimetric method based upon the extraction of salicylic acid with ether and volatilization of the latter at a low temperature. These authors reported that the bromate method was the only one of the three which yielded satisfactory results. This method is based upon the following equations:

$$C_6H_4OH.COOH\ (o) + 8\ Br = C_6H_2Br_3.OBr + 4HBr. + CO_2$$
$$C_6H_2Br_3OBr + 2KI = C_6H_2Br_3OK + KBr + I_2,$$

according to which 8 atoms of bromine per one molecule of salicylic acid must be present although only six are ultimately consumed. In practice it is recommended that at least 75 per cent. excess of bromine be used. Of the seven determinations quoted by Fresenius and Grünhut the first three gave 102.7, 99.6 and 98.1 per cent. of the theoretical 100 per cent. sodium salicylate, the calculated excess amounts of bromate used in the three titrations being respectively 2.00, 1.24 and 1.05 times the amount actually consumed by the salicylate. The remaining four determinations agreed very closely with the amount of salicylate employed, but in these cases the excess of bromate used varied only from 1.15 to 1.26 times the amount uniting with the salicylate. Without further evidence it would therefore appear that concordant results require the use of a fairly definite excess of bromate. The results obtained in the present investigation confirm in general this conclusion, but they furthermore indicate that other factors are involved which seriously impair the reliability of the method.

Of the determinations shown in Table I the first twelve were made with standard thiosulphate and bromate solutions which were equivalent in strengths but not exactly 0.1 *N* since the factor by standardization against resublimed iodine was found to be 1.007, *i. e.*, the readings of each solution multiplied by 1.007 were exactly 0.1 *N*. The standard solutions used for the remaining determinations were accurately 0.1 *N*, the bromate solution being prepared from pure potassium bromate and potassium bromide. The sodium salicylate samples in all cases consisted of carefully recrystallized and dried material of which accurately weighed amounts were dissolved in water and aliquot parts of the solutions corresponding to the weights of salicylate shown in column two of the accompanying table were used. The procedure for each titration was as follows. About 200 cc. of distilled water were placed in a 500 cc. Erlenmeyer flask and the portion of bromate slowly run in from a burette. 10–15 cc. of hydrochloric acid of sp. gr. 1:1 were then added and the salicylate solution introduced. After ten minutes or longer 10 cc. of 10 per cent. potassium

[1] Fresenius and Grünhut, *Z. anal. Chem.*, **38**, 292 (1899).

[2] Freyer, *Chem. Ztg.*, **20**, 820 (1896).

iodide solution were added and the liberated iodine titrated with the 0.1 *N* thiosulphate.

The figures in the fifth column of Table I headed Ratio *a*/*b* show the amount of excess of bromate above that combining with the salicylate to form the insoluble bromine compound. A ratio of 1.0 means that twice as much (that is, 100 per cent. excess) bromate as required to unite with the salicylate was present; a ratio of 0.5 shows that 50 per cent. excess of bromate was used. Fresenius and Grünhut state that at least 75 per cent. excess of bromate should be used but the present results show that in some instances considerably less than this quantity gave approximately correct results.

TABLE I.—SUMMARY OF DETERMINATIONS MADE BY THE BROMATE METHOD OF TITRATING SALICYLATES.

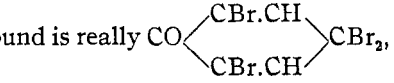
Cc. 0.1 *N* bromate.	Gms. $C_6H_4OHCOONa$.	Cc. 0.1 *N* thiosulphate (*a*).	Cc. 0.1 *N* bromate used (*b*).	Ratio *a*/*b*.	Calc. per cent. $C_6H_4OH.COONa$ found.
50	0.0477	32.26	17.74	1.8	99.22
50	0.0477	32.05	17.90	1.8	98.93
70	0.0954	34.40	35.60	1.0	98.77
40	0.0477	22.05	17.95	1.2	99.45
40	0.0477	22.10	17.90	1.2	99.10
30	0.0477	12.20	17.80	0.7	99.00
50	0.0429	33.70	16.30	2.0	100.00
50	0.0391	35.00	15.00	2.3	103.00
50	0.0782	20.80	29.20	0.7	100.20
50	0.0587	27.50	22.50	1.2	103.00
50	0.0939	14.70	35.30	0.4	100.90
50	0.0782	20.30	29.70	0.7	102.10
50	0.0492	31.70	18.30	1.7	99.10
50	0.0984	13.40	36.60	0.4	99.20
50	0.0594	27.70	22.30	1.2	100.20
50	0.0819	18.80	31.20	0.6	101.60
50	0.0933	14.70	35.30	0.4	101.30
50	0.1070	10.20	39.80	0.3	99.20
50	0.0819	18.80	31.20	0.6	101.70
50	0.0933	14.40	35.60	0.4	101.70
50	0.1070	9.85	40.15	0.25	100.10
50	0.0765	20.80	29.20	0.7	101.90
50	0.0892	16.10	33.90	0.5	101.50
50	0.0765	21.20	28.80	0.7	100.70
50	0.0763	21.60	28.40	0.7	99.30
50	0.1017	12.60	37.30	0.3	97.80
50	0.0763	21.50	28.50	0.7	99.60
50	0.0509	29.90	20.10	1.5	105.40
50	0.0610	25.90	24.10	1.0	105.30
50	0.0712	22.90	27.10	0.8	101.50
50	0.0814	18.70	31.30	0.6	102.40

An examination of the results given in Table I shows that there is a general parallelism between the amount of excess of bromate used in the

titrations and the percentage of salicylate found, but there are a number of exceptions to this rule and in many cases where repeated determinations were made under as nearly identical conditions as possible quite different results were obtained. No satisfactory explanation of this is at present available, and none of my efforts to ascertain the particular conditions under which reliable results could be obtained has proven successful.

Many other determinations than those shown in Table I were made both upon sodium and other salicylates and both with the use of various quantities of hydrochloric acid and potassium iodide solutions but no more concordant results than those shown were obtained.

From the present determinations, which vary from 97.8 to 105.4 per cent. of the theoretical amount of the salicylate present, it may be concluded that the method is capable of yielding only approximately correct results.

There appears some doubt as to just what reaction takes place when bromine acts upon a salicylate in aqueous solution. According to the generally accepted view the insoluble compound which separates is tribrom-phenol-brom, $C_6H_2Br_3OBr$. Thiele and Eichwede[1] have, however, suggested that the formula for this compound is really  , a di-bromo-quinone in which an oxygen atom has been replaced by two bromine atoms.

The Messinger and Vortmann Iodine Method.—This method was proposed by Messinger and Vortmann in 1890.[2] According to it, one molecule of a salicylate unites with three atoms of iodine in an alkaline solution containing at least four molecules of sodium hydroxide per one molecule of salicylate, forming a dark red compound which separated upon warming to 50–60°. The three H atoms replaced by iodine each unite with an iodine atom, consequently in the calculations 6 atoms of iodine per one molecule of salicylate are required. According to the authors the method is applicable to a large number of compounds besides the salicylates with equally satisfactory results.

The experiments of Fresenius and Grünhut,[3] as already mentioned, indicated that the method is unreliable. Some time later however Messinger,[4] replying to Fresenius and Grünhut, claimed that reliable results could be obtained by a careful control of the conditions and gave additional determinations which apparently confirmed his contention.

A few preliminary determinations made in this laboratory gave rather

[1] J. Thiele and H. Eichwede, *Ber.*, **33**, 673 (1900).

[2] *Ber.*, **23**, 2753–55 (1890).

[3] *Loc. cit.*

[4] *J. pr. Ch.* [2], **61**, 237–48 (1900).

unsatisfactory results, and it was decided to examine the method more closely and ascertain if the control of any of the conditions would result in more harmonious and accurate determinations. To this end the effect of the amount of sodium hydroxide present in the solution was first examined. For this purpose a very pure sample of sodium salicylate made in the laboratory from pure sodium bicarbonate and salicylic acid and recrystallized from hot alcohol four times was used. A weighed amount of it, 0.7824 gram, was dissolved in water and diluted to 500 cc. The iodine and sodium thiosulphate standard solutions used for the titrations were equivalent in strength. The readings of each multiplied by 1.008 made them exactly 0.1 *N*. Therefore 1 cc. of the iodine solution was equivalent to 0.002668 × 1.008 = 0.002688 gram $C_6H_4OHCOONa$ (*o*). These same standard solutions were used for all the determinations made by this method.

The titrations were made in 200 cc. graduated flasks. The measured amount of the salicylate and the calculated volume of standard sodium hydroxide solutions were introduced and the standard iodine added slowly while the solution was warmed to 60°. After about 15–30 minutes the mixture was cooled, and acidified with somewhat more *N* sulphuric acid, than necessary to neutralize the alkali used. The solution then diluted to the mark with distilled water, mixed well and filtered. One hundred cubic centimeters of the filtrate were used for the back titration with thiosulphate. The following results show the variations produced by the presence of different amounts of alkali.

Fifty cubic centimeter portions of the salicylate containing 0.07824 gram of sodium salicylate were used for each titration.

Mol. ratio of salicylate : NaOH.	Cc. standard iodine.	Cc. standard thiosulphate for ½ excess.	Calc. per cent. $C_6H_4OHCOONa$.	Remarks.
1 : 2	35	7.0	72.2	White precipitate
1 : 5	35	2.85	100.7	Red precipitate
1 : 10	50	10.1	102.4	Purple precipitate
1 : 25	80	25.75	97.9	Yellow precipitate after acidifying, not before

Since the amounts of sodium hydroxide used in the above titrations gave results which varied over a considerable range, additional titrations were made with the use of quantities of alkali nearer the optimum amount.

The titrations were made upon 50 cc. portions of a sodium salicylate solution containing 1.0282 grams per 500 cc.

These results show that the amount of alkali present can be varied only within very narrow limits. In fact it does not appear possible to always secure trustworthy results even though the ratio of alkali to salicylate is kept reasonably near the theoretical four molecules. Other titrations

were made but the results were no more encouraging than those here given.

Mol. ratio of salicylate : NaOH.	Cc. standard iodine.	Cc. standard thiosulphate for ½ excess.	Calc. per cent. $C_6H_5OHCOONa$.	Remarks.
1 : 4	45	3.35	100.2	(1)
1 : 5	45	2.75	103.3	(2)
1 : 6	45	3.05	101.7	(3)
1 : 8	55	7.75	103.3	(3)

(1) A flocculent reddish precipitate separated.

(2) The precipitate did not flocculate, the filtration was very slow.

(3) No flocculent precipitate could be obtained; a reddish opalescence appeared slowly.

Although the errors produced by the slight variations in the amount of alkali were apparently large enough to condemn the method, it was considered desirable to make some experiments to determine the effect of the variations in the amount of excess of iodine upon the results obtained. For this purpose 50 cc. portions of the sodium salicylate solution used for the preceding titrations were mixed with enough 0.1 *N* sodium hydroxide to have a molecular ratio of 1 sodium salicylate : 4½ sodium hydroxide present in each solution and titrated with the use of an increasing amount of standard iodine solution. The results were as follows: (50 cc. sodium salicylate solution containing 0.10282 gram $C_6H_4OHCOONa$ used for each titration).

Mol. ratio of salicylate : NaOH.	Cc. standard iodine.	Cc. standard thiosulphate for ½ excess.	Calc. per cent. $C_6H_4OHCOONa$.	Remarks.
1 : 4½	41.0	1.45	99.93	(1)
1 : 4½	42.0	1.75	100.40	
1 : 4½	43.5	2.30	101.70	
1 : 4½	45.0	2.90	102.50	
1 : 4½	55.0	7.60	104.10	
1 : 4½	65.0	12.30	105.70	

(1) A red precipitate was obtained in each case but only in the first three titrations did it flocculate after acidifying. In the last three titrations the filtration was very slow and accomplished with difficulty.

It therefore appears that the amount of excess of iodine used in the titration very materially affects the result obtained.

Since the determinations reported by Messinger[1] were made with solutions containing 6 molecules of sodium hydroxide per 1 of salicylate and this proportion was considered by him to be the best, another series of determinations was made with solutions more nearly corresponding to the concentrations employed by Messinger. The sample used was salicylic acid of practically 100 per cent. purity. The weighed amount of it was dissolved in sufficient *N* sodium hydroxide solution to yield sodium salicylate and enough free sodium hydroxide additional to cor-

[1] *Loc. cit.*

respond to 6 2/3 molecules of sodium hydroxide per 1 molecule of sodium salicylate. There was used 1.9464 grams $C_6H_4OHCOOH$ (*o*) and 108 cc. *N* sodium hydroxide per 200 cc. of solution. Twenty-cc. portions of this solution were used for the following titrations:

Gms. $C_6H_4OHCOONa$.	Mol. ratio of salicylate : NaOH.	Cc. standard iodine.	Time before acidifying. Hr.	Cc. thio-sulphate for ½ excess I.	Calc. per cent. $C_6H_4OHCOONa$.
0.2257	1 : 6 2/3	100	½[1]	8.80	98.13
0.2257	1 : 6 2/3	105	½[1]	9.95	101.40
0.2257	1 : 6 2/3	105	1½[1]	9.65	102.10
0.2257	1 : 6 2/3	110	½[2]	11.80	102.90
0.2257	1 : 6 2/3	110	18[2]	11.85	102.80
0.2257	1 : 6 2/3	115	½[2]	14.30	102.90
0.2257	1 : 6 2/3	125	½[3]	18.70	104.30

[1] A faint purple opalescence appeared before, a flocculent yellow precipitate after acidifying.

[2] The solution was purple before and yielded a flocculent red precipitate after acidifying.

[3] A flocculent red precipitate separated even before acidifying.

The differences in time allowed after adding the iodine and before cooling and acidifying as shown for two cases in the preceding results were chosen to show what effect continued contact of the iodine would have upon the amount entering the tri-iodo-salicylate compound. The results are inconclusive since in one case only was more iodine used than with the shorter period of standing.

In none of the last set of titrations did the iodine compound fail to flocculate after rendering the solution acid, while with the preceding determinations three of them did not flocculate and filtration was only accomplished with difficulty. This may possibly be explained by the larger quantities of salts present in the latter experiments.

From the above experiments which were confirmed by many other titrations upon samples of lithium, strontium and other salicylates it may be reasonably concluded that the Messinger and Vortmann iodine method for salicylates is not sufficiently reliable for accurate quantitative results. On the other hand, however, it seems probable that for approximate determinations the method can be made to serve a useful purpose if the limitations pointed out above are fully taken into account.

The Dibromosalicylate Method.—Of the many experiments which were made by the author for the purpose of devising a method for the accurate determination of the salicylic radicle those based upon the formation of dibromosalicylic acid appeared to offer the best prospects of advantageous use.

These experiments demonstrated the fact that by the action of bromine upon salicylic acid in very concentrated hydrochloric acid solution four atoms of bromine per 1 molecule of salicylate are required, dibromosalicylic

acid being formed and no oxidation or other change taking place. The details of the method as first devised are as follows: the weighed sample of salicylate, dissolved in a few cc. water or an aliquot portion of the solution of the sample, is placed in a 200 cc. glass stoppered bottle and about 50 cc. strong hydrochloric acid added. The titration is then made with 0.2 *N* bromate solution, shaking the bottle, and warming gently between each addition of bromate until the yellow color of the excess of bromine persists five minutes after the addition of the last two drops of the standard solution, the temperature having reached 80–100° in the meantime. A number of titrations made in this manner upon carefully recrystallized sodium salicylate yielded nearly theoretical results when calculated on the basis of four atoms of bromine per one molecule of salicylate. The identity of the dibromosalicylic acid precipitate was established in each case by a melting point determination which was found to lie between 218° and 220°: the precipitates were also tested by means of a drop of ferric chloride which produced the intense purple color characteristic of salicylic acid.

The titrations were as follows:

$C_6H_4OHCOONa$.				
cc.	Gm.	Cc. conc. HCl.	Cc. 0.2 *N* bromate.	Calc. per cent. $C_6H_4OHCOONa$.
2.0	0.0739	50	9.3	100.7
3.0	0.1109	25	13.8	99.6
4.0	0.1479	50	18.35	99.3
5.0	0.1849	25	23.20	100.5
6.0	0.2218	50	27.50	99.3
3.0	0.0863	50	10.70	99.3
3.0	0.0863	50	10.80	100.2
3.0	0.0863	50	10.90	101.2
5.5	0.1582	50	19.50	98.7
7.0	0.2013	50	25.60	101.8

Although these results are somewhat variable they are fairly satisfactory when it is considered that a difference of 0.1 cc. of the standard bromate solution corresponds to approximately 1 per cent. salicylate, and also that the samples of salicylate were measured in volumes of 2 to 7 cc.

The method, however, has a number of defects and is therefore offered only as a possible substitute for the methods shown in the preceding sections of this paper to be unreliable. The time required for a titration is considerable since the reaction proceeds especially slowly towards the end and the disappearance of the bromine color must be awaited after the introduction of each fresh portion of the bromate solution. Furthermore the exact end point must be fixed more or less arbitrarily and this offers opportunity for considerable variations due to the individuality of the analyst. The results given in the accompanying table vary

from 98.7 to 101.8 per cent. but it is probable that this variation can be reduced to about one-half by more experience.

Efforts so far made to improve the method have been only partially successful and will therefore be described briefly. After a number of experiments it was found that an aqueous solution of the salicylate added to a concentrated hydrochloric acid solution of bromine yielded dibromosalicylate, and that the excess of bromine could be estimated with standard stannous chloride solution. The hydrochloric acid solution of bromine was made by adding enough bromine to concentrated hydrochloric acid to yield a dark red-brown colored liquid. The insoluble material was filtered out by means of an asbestos mat and the solution standardized with 0.1 *N* thiosulphate as follows: about 300 cc. of water are placed in an Erlenmeyer flask and the measured portion of the hydrochloric acid solution of bromine gradually introduced. About 10 to 15 cc. of 10 per cent. potassium iodide solution are then added and the liberated iodine titrated to loss of color with thiosulphate. The stannous chloride solution is standardized by titrating against the hydrochloric acid bromine solution. A measured volume of the latter being placed in a glass stoppered bottle and the stannous chloride added gradually until the bromine color is discharged. It is of course necessary to standardize the above solution each day they are used for determinations of salicylates The character of the results which may be obtained is illustrated by the following determinations.

The standard solutions:

Fifty cc. HCl solution of Br required 49.4 cc. 0.1 *N* sodium thiosulphate.

Fifty cc. HCl solution of Br required 19.9 cc. 0.1 *N* stannous chloride. The salicylate solution contained 1.0253 grams of purified $C_6H_4OHCOONa$ per 200 cc.

Titrations:

Cc. conc. HCl solution of Br.	Cc. of salicylate solution.	Cc. $SnCl_2$ solution for excess Br.	Cc. conc. HCl, sol. of Br used.	Calc. per cent. of $C_6H_4OHCOONa$.
50	25	7.35	31.54	97.34
50	20	9.8	25.39	97.95
50	15	12.4	18.85	96.96
50	10	14.8	12.82	98.91
50	25	7.3	31.68	97.50
50	20	9.75	25.50	98.06
50	15	12.35	18.98	97.31
50	10	14.75	12.94	99.51
50	20	9.65	25.76	99.06
50	10	14.75	12.85	98.81
50	20	9.65	25.76	99.06
50	10	14.75	12.85	98.81

In the first four determinations approximately one-half hour was allowed before the back titration with the stannous chloride was made.

In the second four this time was an hour. In the last two determinations only about five minutes were allowed but the solutions were heated to about 60° before the back titration.

It will be noticed that all the results are somewhat low and it may therefore be concluded that the reaction did not run quite to the end.

In addition to these experiments upon the dibromosalicylic acid reaction, many unsuccessful attempts to find other reactions upon which to base a determination of the salicylic radicle were made. Among these may be mentioned the experiments upon:

(*a*) *Acetylization Methods.*—The acetylization apparently goes well enough and the yield of the acetyl salicylic acid (aspirin) is no doubt quantitative but the estimation of this latter compound offers no particular advantage over the unchanged salicylate. It could not be filtered out and determined gravimetrically nor titrated to a satisfactory end point with bromate. Failure also followed a modification based upon acetylization with acetyl chloride and after removing the excess of the latter by careful evaporation at low temperature, weighing the acetylized product.

(*b*) *Bromate Gravimetric Methods.*—The compound formed by passing bromine vapor through a dilute aqueous solution of a salicylate was found to be too soluble for its successful removal, and furthermore it could not be dried to constant weight.

(*c*) *Modified Bromate Volumetric Methods.*—Among these may be mentioned attempts to determine the hydrobromic acid formed by passing bromine vapor through an aqueous solution of a salicylate. Also the iodine titration of the filtered and washed precipitate and of the filtrate from this precipitate.

(*d*) *Silver Salicylate Precipitation Methods.*—Both volumetric and gravimetric modifications were tried but without success on account of the solubility of the silver salicylate in the aqueous solution.

Although the experiments mentioned above have all yielded negative results it is hoped that this brief mention of them may prove helpful to others who may have opportunities to study methods for the determination of salicylates.

Conclusion.—The bromate method of Freyer and the iodine method of Messinger and Vortmann are shown to be of uncertain reliability for the quantitative determination of the salicylic radicle. A new reaction by which dibromosalicylic acid is formed almost quantitatively by the action of bromine upon salicylates in concentrated hydrochloric acid solution, is described and methods based upon this reaction which yield fairly definite results are suggested.